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EDITORIAL COMMENT

Bivalirudin in Acute Myocardial Infarction: *"Primum Non Nocere"*

The Eternal Dilemma: Balancing Risks and Benefits in High-Risk Patients*

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Primary angioplasty has been enthroned as the cornerstone of therapy in patients with ST-segment elevation myocardial infarction (STEMI) (1–3). In this scenario, coronary stenting is systematically offered. While drug-eluting stents (DES) are becoming increasingly used in STEMI patients because of their superior efficacy profile (1), safety concerns remain, and bare-metal stents (BMS) are still preferred by some investigators in this highly thrombogenic milieu (3).

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Adjuvant pharmacological therapy remains another critical issue (1–3). The unprecedented advances in antithrombotic therapy occurring in the last decade have led to dramatic improvements in reperfusion success, both at the epicardial and microvascular level, and more importantly, to superior clinical outcomes (1–4). However, the aggressive antiplatelet therapies recommended for the highly instrumented STEMI patients may act as a double-edged sword, leading to increased hemorrhagic complications (1,2). Currently, major bleeding is feared as 1 of the most important noncardiac complication in these patients (4,5). In fact, not only anemia and bleeding but also transfusion requirement have been independently associated with major adverse events and mortality after coronary interventions (4,5). In STEMI patients in particular, prevention of bleeding (mainly iatrogenic and related to the femoral access) is currently considered of paramount importance (4,5). Of interest, recent studies suggest that bivalirudin is not only uniquely safe but also cost effective in patients with a high bleeding risk (6).

Therefore, further insights into the optimal adjuvant antiplatelet and antithrombotic regimens are urgently required to refine clinical practice in this challenging setting. In this issue of *JACC: Cardiovascular Interventions*, a report from the HORIZONS-AMI (Harmonizing Outcomes With RevasculariZatiON and Stents in Acute Myocardial Infarction) investigators (7) suggests that for "high-risk" STEMI patients undergoing primary interventions, bivalirudin reduces both mortality and recurrent myocardial infarction as compared with unfractionated heparin (UFH) plus glycoprotein IIb/IIIa inhibitors (GPI).

The HORIZONS-AMI in perspective. Bivalirudin is especially attractive for STEMI patients undergoing primary angioplasty procedures. A retrospective study suggested that, when GPI are not used in this scenario, both bivalirudin and UFH showed equivalent efficacy and safety profiles (8). However, the benefits of GPI are well established for these patients, despite the increase in bleeding risks (9). Of note, for patients undergoing primary angioplasty, the prognostic implications of major bleeding are as important as reinfarction (1,2,4). The large HORIZONS-AMI trial provided important novel evidence for the management of patients with STEMI undergoing primary interventions (1,2). The 2 coprimary end points of this trial were: 1) major bleeding; and 2) a combination of major bleeding and net adverse clinical events (including death, reinfarction, ischemia-driven target vessel revascularization, and stroke) (1,2). The HORIZONS-AMI study demonstrated that bivalirudin compared with UFH+GPI decreased major bleeding and, importantly, 30-day and 1-year mortality (1). Bivalirudin also reduced late (>30 days) cardiac mortality and reinfarction rates (2). An increased risk of acute stent thrombosis (pre-specified event) was initially detected in the bivalirudin group, but this risk signal disappeared at 30 days and 1 year (1,2). Since then, a major change in the landscape has occurred for STEMI patients, and many investigators considered bivalirudin monotherapy as the standard of care during primary angioplasty procedures. However, economic factors, prevailing doubts regarding efficacy, and a high use of the radial artery access (10), together with "unscientific" reluctance to change, remain barriers preventing a wider utilization of this new agent during primary interventions in many countries.

Contributions of the present study. The objective of the current study by Parodi et al. (7) was to assess the relationship between 1-year mortality and baseline patient risk. Accordingly, the previously validated CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) risk score (11) was used to classify STEMI patients into low (1,522; 60%), intermediate (531; 21%), and high risk (477; 19%). Interestingly, in the high-risk subset, bivalirudin significantly reduced 1-year mortality and recurrent myocardial infarction as compared with UFH+GPI. These findings are of major clinical

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interest and reinforce the evidence supporting the value of bivalirudin in STEMI patients. However, some methodological issues should be discussed.

First, although the benefit found for high-risk patients was robust and unquestionable, no apparent efficacy benefit could be demonstrated for patients with low to intermediate risk who actually accounted for 81% of patients in the trial (7). Thus, further studies should elaborate on the potential value bivalirudin in "unselected" real world patients with STEMI.

Second, subgroup analyses tend to identify major benefits in highly selected patient cohorts. In this situation, the potential for bias or chance findings persists despite carefully adjusting for multiple testing. This potential is relevant considering that even the main trial was unpowered to detect reductions in mortality (although actually this was the case) (1,7).

Third, the reduction of bleeding complications with bivalirudin was only significant in the low-risk group, and that may be perceived as counterintuitive. Considering the CADILLAC risk score, one would anticipate that bleeding risks would also be higher in high-risk patients and that, for this subset, bivalirudin would be particularly effective. Sample size constraints may explain this apparent paradox because, actually, bivalirudin decreased bleeding estimates across all risk strata, although the difference was only statistically significant for low-risk patients, who accounted for 60% of the population (7). The finding of a distinct treatment effect depending on the selected outcome (death/myocardial infarction versus bleeding) led these investigators to hypothesize that among high-risk patients, the mortality reduction induced by bivalirudin cannot be solely explain by its effects on bleeding. Further, two-thirds of patients assigned to bivalirudin received upfront UFH and a 600-mg clopidogrel loading dose, and 7.5% of patients eventually received GPI (1). Whether these adjuvant strategies impacted in the outcome of high-risk patients remains unclear.

Fourth, the 2 strategies concurrently examined by the HORIZONS-AMI factorial design (DES/BMS and bivalirudin/UFH+GPI) have major economic implications (1). Considering than DES and bivalirudin were demonstrated to be superior to their comparators, information on long-term cost-effectiveness, particularly in high-risk patients, would have been of major interest, and warrants additional studies.

Fifth, although the value of the CADILLAC risk score has been established (11), some of the requested items were not available in the HORIZONS-AMI study. Nearly one-third of patients (1,072) could not be risk stratified according to this score because of missing data, mainly left ventricular angiography (7). Whether noninvasive assessment of left ventricular function may be used as a surrogate for angiographic ejection fraction, without affecting the predictive value of the model, remains undefined. Besides, it remains likely that the number of unclassifiable patients would be higher during routine clinical practice than in a randomized clinical trial. Furthermore, major differences were found between patients included in the present analysis and those unclassifiable. Indeed, "excluded" patients had a risk marginally higher than that seen in the CADILLAC study-derived "intermediate risk" subgroup (7).

Last but not least, in the HORIZONS-AMI study, emergency coronary angiography was performed after randomization to the corresponding antithrombotic therapy, which was started in the emergency room (1). However, of the 7 variables used by the CADILLAC risk score, 4 are readily available before catheterization (age, anemia, renal failure, and Killip class), but 3 of them (left ventricular ejection fraction, multivessel disease, and final TIMI [Thrombolysis In Myocardial Infarction] flow grade) can only be identified during or after the procedure, once the selection of the antithrombotic strategy may have been made. This may be considered as a caveat of this score for the selection of patients most likely to benefit from bivalirudin therapy. These potential limitations notwithstanding, the current study extends our knowledge and provides strong evidence in favor of bivalirudin for high-risk STEMI patients (7).

Subgroup analyses: is the devil in the detail? The present study represents a post-hoc subgroup analysis of the large HORIZONS-AMI trial (7). Most subgroup analyses are performed from negative trials to identify patient subsets with potential clinical benefits. Therefore, attempts to identify the cohort of patients experiencing most of the benefit from a positive trial deserve special recognition, and the authors should be commended for this scientific endeavor. Conventional wisdom suggests that in randomized clinical trials, only the primary end point should be considered to generate evidence-based scientific knowledge. This appears to be an adequate premise, considering that the primary end point determines the sample size calculation required to address the study's hypothesis. Accordingly, the additional information obtained by pre-specified secondary end points, pre-defined subgroup analyses, and post-hoc studies (theoretically in decreasing order of scientific merit) should be considered as exploratory or hypothesis generating. However, is it all that simple?

Most current cardiovascular trials select composite end points as the primary outcome measure (12,13). Composite end points are highly effective to reduce sample size requirements, to avoid bias of competitive risks, and to assess the net effect of competing interventions. However, when significant heterogeneity exists among their individual components (regarding clinical relevance, number of events, and magnitude of treatment effect), the risk of misinterpretation increases (12,13). Some of these occurred in the HORIZONS-AMI study. Would any patient or physician consider stroke and bleeding of similar relevance? As in most randomized clinical trials, frequencies of individual events were largely different, and the effect of interventions varied among the components of

the combined end point. For instance, in this substudy (7) and in the main HORIZONS-AMI trial (1,2), there was a nonsignificant trend for higher revascularization rates after bivalirudin, among non–high-risk patients and among all patients, respectively. Similarly, although from a different clinical setting, a signal for a higher rate of myocardial infarction after bivalirudin was detected in the ISAR-REACT-3 (Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment-3) study and in a recent meta-analysis (14,15). If that were the case, the benefits of bivalirudin in reducing bleeding risks might be offset by a lower efficacy to prevent myocardial infarction (14,15). Under these circumstances, our confidence to assess the real treatment effect by exclusively assessing the results of the combined primary end point is limited (12,13). It is precisely in this context where subgroup analyses emerge as a powerful tool to fully characterize clinical factors significantly affecting treatment effects (12,13). Thus, the current analysis of the HORIZONS-AMI trial provides scientifically valuable, novel, and unique insights that help to further refine interventions in high-risk patients with STEMI.

Final remarks. The eternal therapeutic dilemma, balancing risks and benefits for high-risk patients, remains unresolved. Is doing more good than harm better than *primum non nocere*? Nowadays, costs should also be included in the equation. When analyzing results of interventions in high-risk patients, safety issues are of paramount importance, and therefore, complications and their potential causes should be carefully collected, openly disclosed, and critically scrutinized. *Primum non nocere* (first, not to harm) and *secundus, opinio vulnero* (second, report the harm) may, therefore, be equally important. When adequately performed, subgroup analyses provide unique insights not available by other methods. The HORIZONS-AMI study strictly adhered to these general principles and provided adequate guidance to optimize interventions in high-risk STEMI patients. For these patients, bivalirudin appears to be not only safer but also more effective than standard antithrombotic strategies and, therefore, should be considered the preferred option. Further investigation is now warranted to assess the value of bivalirudin for patients receiving novel, more predictable, and potent antiplatelet agents.

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